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BOSTON UNIVERSITY
GRADUATE SCHOOL

Thesis

CONDENSATIONS OF SECONDARY AMINES
WITH
FORMALDEHYDE AND NITROPARAFFINS.

THE MANNICH REACTION

By

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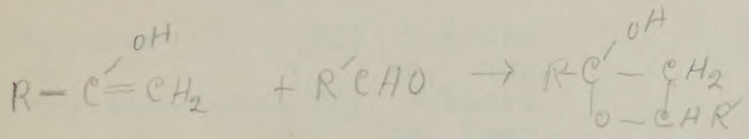
INTRODUCTION

The Mannich Reaction (1) has been described as one in which ammonia or an amine is condensed with formaldehyde, and a compound containing a reactive hydrogen. In this work, the nitroparaffins were used to furnish the reactive hydrogen. If a primary or a secondary amine is used in the condensation, then a secondary or tertiary nitro amine will be produced. The exact mechanism of this condensation has not been definitely established. K. Bodendorf and G. Koralewski (2) have recently made studies on the condensations with the intention of establishing the mechanism involved.

They concluded that neither the methylol compounds of the ketones nor those of the amines represent the real intermediate products. Instead they believe that the aldehyde-ketone condensation takes place by means of the following mechanism:



$$R-\overset{OH}{C}=CH_2 + R'CHO \rightarrow R\underset{O-CHR'}{\overset{OH}{C}-CH_2}$$

According to which the ketones assume the enol form. For a clearer understanding and appreciation of their work the following table compiled by them is herein presented:

Table I

Reactants	Conditions	Yield in Grams	% Yield
Antipyrine + HCHO + dimethylamine	24 hours rm. temp.	15	60
Antipyrine + Dimethylaminomethanol	24 hours rm. temp.	11	45
Antipyrine + Formaldehyde + Salt of Dimethylamine	24 hours rm. temp.	21	85
Antipyrine + Formaldehyde + Piperidine	(1) 2 hours rm. temp.	10.7	37
	(2) 4 hours rm. temp.	12.5	44
Antipyrine + Piperidinomethanol	(1) 2 hours rm. temp.	5.8	20
	(2) 4 hours rm. temp.	9.5	33
Antipyrine + Formaldehyde + Salt of Piperidine	(1) 2 hours rm. temp.	18	62
	(2) 4 hours rm. temp.	20.2	70
Cyclohexanone + Formaldehyde + Piperidine	8 days rm. temp.	7.2	36
Cyclohexanone + Piperidinomethanol	8 days rm. temp.	5.2	26

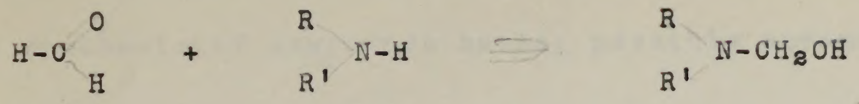
It is of interest to note that only ketones were used as the compounds furnishing the reactive hydrogen. The piperidino methanol (3) and the morpholino methanols have been shown to be very reactive whereas the reaction between nitroparaffins and formaldehyde are apparently not as reactive, in fact a catalyst is usually required. Hass (4) recommends approximately 43 hours in the presence of an alkali for the condensation between formaldehyde and a nitroparaffin.

For a general idea of the reactivity of these alkylamino methylols we can look back to the fact that the piperidino methanol was reported by Henry (5) and used by him to react with different compounds such as dibenzylamine, piperidine and dinitropropane. Mason and Zief (6) in their condensations, separated the morpholine methanol, identified it, and proceeded to react it with a large number of compounds including morpholine, piperidine and dicyclohexylamine.

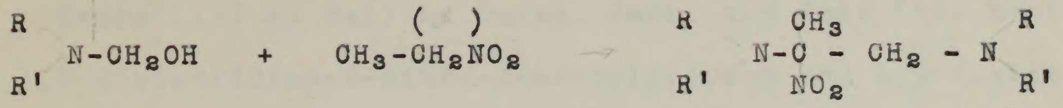
It therefore does not seem unreasonable to expect these alkylamino methanols to react by the same mechanism with compounds containing reactive hydrogen splitting out a molecule of water during the process.

In consideration of the compounds used by Bodendorf and Koralewski (7), it is believed that the study should be extended to other types of compounds containing reactive hydrogen, before any conclusions regarding the condensation mechanism can be drawn. However, on the basis of Henry's work (8) and our own, the following postulated mechanism serves as a useful

means of explaining the reactions.



$$H-C\overset{O}{\underset{H}{}} + \overset{R}{\underset{R'}{}}N-H \longrightarrow \overset{R}{\underset{R'}{}}N-CH_2OH$$



$$\overset{R}{\underset{R'}{}}N-CH_2OH + \overset{(\ \ )}{CH_3-CH_2NO_2} \longrightarrow \overset{R}{\underset{R'}{}}N-\overset{CH_3}{\underset{NO_2}{C}} - CH_2 - N\overset{R}{\underset{R'}{}}$$

Louis Henry (8) observed that the alkylamino methanol produced by the addition of an amine to formaldehyde would react with either nitromethane or nitroethane to replace the alpha hydrogen atoms of the nitroparaffin with the alkylamino methyl group. Duden, Bock, and Reid (9) and Louis Henry (10) are in agreement in concluding that one mole of nitromethane or nitroethane would react with two moles of piperidine and two moles of formaldehyde. More recently, on the basis of studies of the reaction of secondary amines with formaldehyde and certain nitroparaffins, Cerf de Mauny (11) postulated the rule that the number of alkyl amino methylols that would react with a nitroparaffin is one less than the number of hydrogen atoms linked to the carbon to which the nitro group is attached. The nitroparaffins that he worked with were nitromethane, 1-mitropropane and 1-nitrooctane. Mason and Zief (12) showed that two molecules of morpholino methanol reacted with one molecule of nitroethane, thus confirming Henry's observations and making nitroethane an exception to Cerf de Mauny's rule.

It is the intention in this work to apply these reactions to the synthesis of compounds having possible antimalarial value.

Henry (13) as well as Duden, Bock, and Reid (14) mentioned 1,3-dipiperidino-2-nitro-2-methylpropane and 1,3-dipiperidino-2-nitropropane but did not give any experimental data regarding their preparation, yield, properties, nor whether the former compound was reduced. A search through Beilstein and Chemical Abstracts was equally unsatisfactory nor was any mention of the former compound made. Therefore, in our studies on the condensation of secondary amines with formaldehyde and nitroparaffins, data on the above mentioned piperidino compounds are included.

Condensations of Piperidine
with
Formaldehyde and Nitroparaffins.

In as much as some work had been previously performed on the reactions of piperidino-methanol with nitroparaffins, these reactions are considered first.

In order to avoid a too lively reaction the concentration of the formaldehyde was maintained below thirty per cent. Following the suggestion of Cerf de Mauny the temperature of the reaction was kept below 20°C. This is in accordance with the findings of Cerf de Mauny and Tseon Heou-Feo (15) that the methyloldiethylamine, save in the presence of excess formaldehyde, is transformed by heat to methylene bis diethylamine which does not react with nitromethane.

It was observed that the rate of addition of the nitroparaffin had no appreciable effect on the yield.

Condensation of Piperidine
with
Formaldehyde and Nitromethane

Experiment 1.

To 17.5 cc. of a cold solution of 37% formaldehyde mixed with 5 cc. of water was added dropwise 17 grams of piperidine. Heat was evolved and oil globules of piperidinemethanol separated to the surface. One-tenth mole of nitromethane was added slowly. The resulting milky white mixture changed to a white solid mass in three to five minutes. The precipitate was filtered, washed with distilled water on a Buchner funnel and dried. The crude yield was 32.1 grams. This precipitate was fairly unstable and gradually assumed a light tan color on standing. A characteristic odor resembling that of piperidine was detected. Recrystallizations from water and alcohol were unsatisfactory. The compound rapidly decomposed in warm alcohol. An ether solution of the precipitate mixed with charcoal (because of the tan color of the solution) was filtered and the filtrate allowed to evaporate spontaneously. Whitish, buff tinged colored, needle-like crystals were obtained which melted at 83-85°C.

Experiment 2.

To 9 cc. of a cold solution of 37% formaldehyde (0.1 mole) mixed with 5 cc. of water, was added dropwise 8.5 grams (0.1 mole) of piperidine and the mixture stirred. To this was added rapidly a solution of 3.1 grams (.05 moles) of nitromethane dissolved in 30 cc. of water. A thick slushy mixture of a white precipitate formed in about three minutes. The precipitate was washed on a Buchner funnel, pressed between filter paper and weighed. The crude yield was 17.9 grams. This was allowed to stand overnight in a vaccuum desiccator where it turned to a buff color indicating that some decomposition may have occurred. The material was dried on a clay plate, powdered and its melting point determined. It melted at 89.5-90.5°C. (corr.). The weight of this dried product was 9.8 grams. The yield was 77.1%.

An ether solution of this precipitate, mixed with Norit was filtered and the ether allowed to evaporate spontaneously. Long needle-like buff colored crystals were obtanied. These were dried on a clay plate and a melting point determined. It was found to be 83-85°C., indicating the presence of impurities.

Experiment 3.

The same procedure as used in Experiment 2 was followed. The white precipitate (crop 1) was washed with cold distilled water, dissolved in cold absolute alcohol and this solution diluted with sufficient distilled water until a 40% alcoholic solution was obtained. The 1,3-dipiperidino-2-nitropropane was reprecipitated (crop 2). This was filtered and part of it was dissolved in alcohol and reprecipitated as before. (crop 3). These three crops were dried on a clay plate and their melting points determined.

Crop 1	Melted at 90-93°C. (Corr.)
Crop 2	Melted at 93.75-94.20°C. (Corr.)
Crop 3	Melted at 94.8-95.4°C. (Corr.) (Det. 1) 93.6-94.2°C. (Corr,) (Det. 2)

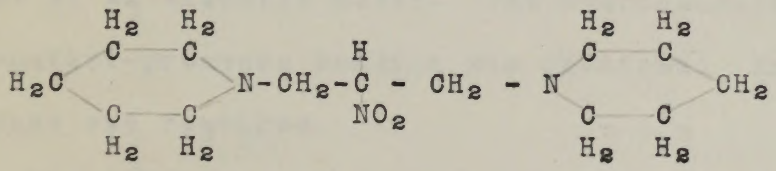
Crop (2) of 1,3-dipiperidino-2-nitropropane was considered sufficiently pure so that neutral equivalent and molecular weight determinations were made in order to establish the identity of this compound.

The neutral equivalent method was found to be unsatisfactory for the end-point of the titration with a standardized acid was very poor.

The molecular weight was determined from the depression of the freezing point of benzene. The method followed was that described in Daniels, Mathews and William's Experimental Physical Chemistry (16).

Calculated molecular weight		255
Found	det. (1)	233
	det. (2)	222
Average molecular weight		228

The difference between the calculated molecular weight and the determined weight may be due to insufficient purity of the compound. However, this value eliminates all other compounds.which could possible be produced. It is interesting to note that Henry (17) obtained a value of   by means of the same method. This conclusion agrees with Henry's findimgs that the compound is 1,3-dipiperidino-2-nitropropane and has the following structure:



Reduction of 1,3-Dipiperidino-2-Nitropropane.

Experiment 1.

Of a batch of 1,3-dipiperidino-2-nitropropane recrystallized from 95% alcohol and having a melting point of 89.5-90.5°C. (corr.) 10.5 grams was used for catalytic reduction. This was placed into a twelve-ounce, thick, glass bottle together with 225 cc. of 95% alcohol. Eight grams of Raney Nickel activated by the method of Covert and Adkins (18) was then added. The bottle was then attached to a Parr Hydrogenation Apparatus of the low pressure type. The air was removed, hydrogen then admitted and the contents of the flask subjected to 45 lbs. pressure. During the hydrogenation the bottle was agitated by means of an electric motor. The hydrogenation was continued until a constant-pressure reading was obtained. In this case forty minutes was required.

The solution was then filtered and the alcohol removed by means of a steam-bath and a fractionation column. The residue was then distilled at 2 mm. pressure and 135°C. A colorless liquid with a faint greenish tinge distilled. A yield of 3.5 grams (33.3%) was obtained.

Analysis of this reduction product: Kjeldahl

	Weight of Sample	0.0936 N HCl	0.1238 N NaOH	%Nitrogen
I	.4754 grams	70 cc.	22.37 cc.	17.90
II	.1664 grams	35 cc.	3.63 cc.	17.87

Calculated for $C_{13}H_{27}N_3$ 18.64 % Nitrogen

Preparation of Activated Raney Nickel

Three-hundred grams of sodium hydroxide was dissolved in 1200 cc. of distilled water. The solution was divided into two portions and placed into two 2-liter beakers immersed in ice-baths. To each portion was added slowly (nearly three-hour period) 150 g. of Raney Nickel (Nickel-aluminum alloy). The mixtures were heated on separate hot plates for one hour at 115-120° C., allowed to stand overnight, and then heated an additional three hours. Two-hundred cubic centimeters of 19% solution of sodium hydroxide were then added and the mixtures heated for about three hours and then diluted to one and one-half liters.

The supernatant liquid was decanted and the suspension washed eight times by decantation, then alternately by decantation and on a Buchner funnel with distilled water until the filtrate was neutral to litmus paper. The nickel was then washed with 95% alcohol 3-4 times and stored in a glass stoppered bottle under absolute alcohol.

Condensation of Piperidine with Formaldehyde and Nitroethane.

Experiment

To 32 cc of a cold solution of 37% formaldehyde was added dropwise 34 grams of piperidine. Fifteen and two-tenths grams of nitroethane was then added fairly rapidly and the mixture stirred. Two layers formed. After allowing the mixture to stand approximately six to seven hours with occasional stirring, the mass solidified. This was then allowed to stand overnight. The next day the mass was filtered on a Buchner funnel and washed twice with cold absolute alcohol. The product was then recrystallized from absolute alcohol. (Crop 1). Some of the alcohol of the filtrate boiled off due to the suction of the water aspirator and a second crop was obtained from the precipitated material. This was filtered and washed with alcohol. The filtrate was diluted with water until a fifty per cent alcoholic solution resulted. A third crop was thus produced.

All three crops were dried, weighed and the melting points determined.

	Weight	Melting Point
Crop (1)	25 grams	99-101°C. (corr.)
Crop (2)	12 grams	99.5-101.5°C.
Crop (3)	9.8 grams	99.9-101°C.

46.8 grams total yield (97.9%)

This melting point was slightly higher than that found in Richter's Lexikon der Kohlenstoff Verbindungen for 1,3-dipiperidino-2-nitro-2-methylpropane, which was 98-99°C.

Reduction of 1,3-Dipiperidino-2-nitro-2-methylpropane.

Experiment 1.

Seventeen and two-tenths of 1,3-dipiperidino-2-nitro-2-methylpropane (melting point 99-101°C.) was mixed with 245 cc. of 95% alcohol and hydrogenated as before for one hour and twenty minutes at forty-five to fifty pounds pressure. Considerable heat was evolved. The mixture was then filtered and the alcohol removed by means of a steam-bath. At two millimeters pressure, a clear colorless liquid distilled over at 60-61°C. (Fraction I). At 135°C., a clear viscid slightly greenish-yellow liquid (Fraction II) distilled over. The yield of this latter fraction was 4.1 grams or 23%.

Analysis of This Reduction Product-Fraction II-Kjeldahl

Det.	Wt. of Sample	0.0936 N HCl	0.1244 NaOH	% Nitrogen
I	0.4448	75 cc.	13.6 cc.	16.9
II	0.6023	100 cc.	42.25 cc.	16.8

Calculated for $C_{14}H_{29}N_3$ N equals 17.55 %

Experiment 2.

Twenty grams of 1,3-dipiperidino-2-nitro-2-methylpropane (melting point 99-101°C.) was added to 175 cc. of 95% alcohol. Ten grams of Raney Nickel was added and the mixture then warmed. The hydrogenation was performed at 45 lbs. pressure for 1.5 hours with the evolution of considerable heat. The

mixture was heated, the alcohol removed by means of a steam-bath and a crude yellowish liquid residue of 12 grams was obtained.

At first, the pressure could not be reduced below 21 mm. at 27°C. Then the pressure dropped to 10 mm. After raising the temperature of the oil-bath to 70°C., the pressure dropped to 4-3.5 mm. These changes in pressure indicate that some vapor may have passed through the system. The liquid was then distilled.

Fraction	Weight	B.P. Range	Oil Bath Range (Deg. C.)
I	1.1	57	107-135-155
II	2.9	138-139	198-200
Trap	1.8		
Residue	Approx. 1.5-3 g.		

Experiment 3.

Twenty grams of 1,3-dipiperidino-2-nitro-2-methylpropane (melting point 99-101°C.) was mixed with 150 cc. of absolute alcohol and the mixture hydrogenated at fifty-five pounds pressure. Much heat was evolved. After removing the nickel and alcohol, the residue was distilled at 16 mm. pressure in an atmosphere of air. A fraction distilled at 80°C. and weighed 1.7 grams. The residue was approximately 2-3 grams.

Fraction I of 1,3-dipiperidino-2-amino-2-methylpropane reduction mixture (B.P. 80°C. at 16 mm.) was redistille at 52°C. (oil bath 75-85°C.) at 0.3 mm. pressure.

Samples of this low boiling fraction obtained from reduction of 1,3-dipiperidino-2-nitro-2-methylpropane were combined and their weight determined to be 7 grams. This combined mixture was then redistilled in an atmosphere of air at 0.8 mm. pressure. Drops began distilling at 48°C. (oil-bath 62°C.) and came over freely at 49°C. (oil-bath 69°C.) The residue was about 0.5 - 1 gram.

This distillate was then redistilled at 95.8 mm. pressure.

Fraction	Weight	Pressure	B.P.	Oil-Bath Range
I	0.5	95.8	117.5	162-161
II	4.0	85,83,80 75,70	116,116, 115,113.9 112.5	154.5, 154,156 156.2, 157

Residue 0.5 - 1 gram approx.

The above fraction II was then used for analysis.

Experiment 4.

Twenty grams of 1,3-dipiperidino-2-nitro-2-methylpropane (M.P. 99-101°C.) mixed with 150 cc. of absolute alcohol and 35 grams of Raney Nickel was hydrogenated at 55 lbs. pressure. Much heat was evolved. After removing the Raney Nickel and alcohol, the residue was distilled at 16 mm. pressure.

Fraction	Weight	Boiling Point	Oil-Bath Range
I	1.7 g.	80	163-170
II	0.8 g.	80	193-212

Residue 2. - 3 grams which decomposed.

The yield was 12.5%.

Due to the production of a relatively large amount of low boiling fraction of the reduced compound and a small yield of the higher boiling fraction (desired) it was believed that Hydrogenol hydrolysis had occurred. An investigation in order to determine the identity of the low-boiling fraction was then undertaken.

Low-Boiling Fraction II of Exp. 3

B.P. 56-59°C. at 0.5 mm. pressure.

Elementary analysis - positive tests for nitrogen

Physical Properties

Colorless with a slight yellowish green tinge, liquid, basic, amine odor.

Solubility

Water-readily soluble

Ether-readily soluble

HCl (5%) - soluble with heat evolved

NaOH (5%) - insoluble

These tests indicate a low molecular weight amine.

Hinsberg Test

This unknown compound (0.3 cc.) was mixed with benzenesulfonyl chloride and sodium hydroxide and the mixture shaken. Heat was evolved. A whitish oily mixture resulted, which separated to the bottom on standing. The solution was then filtered. To the filtrate then was added hydrochloric acid. A white precipitate, soluble in sodium hydroxide and

hydrochloric acid, was obtained.

The precipitate could not be removed by filtration and on standing it redissolved.

The molecular weight was determined by the depression of the freezing point of benzene. Results.

	Weight of Sample	Wt. of Benzene Used	Depression of Freezing Pt.	Molecular Weight
I	0.2929	17.448	0.64	134
II	0.3160	17.448	0.666	139

The formula used is

$$\text{Mol. Wt.} = \frac{1000 \times 5.12 \times \text{wt. sample used}}{\text{Wt. of solvent} \times \text{Depression of Freezing Point}}$$

Low Boiling Fraction

B.P. 56-59°C. at 0.5 mm. pressure

Neutral Equivalent

By means of a pycnometer a weighed amount of the sample was transferred to a 250 cc. flask containing 100 cc. of distilled water. A drop of the indicator was added and the solution titrated with standard acid. Data.

Det.	Wt. of Sample	0.0942 N HCl	Indicator	Neutral Equiv.	Mol. Wt.
I	0.3146	44.5 cc.	Methyl Red	75.1	150.2
II	0.2057	29.0 cc.	Methyl Orange	75.2	150.4

The end points were not sharp, and therefore very poor. The formula used was

$$\text{Neutral Equivalent} = \frac{\text{Wt. of sample} \times 1000}{\text{Normality of acid} \times \text{cc. of acid used}}$$

The molecular weight was obtained by multiplying the neutral equivalent by the number of amine groups believed to be present.

Kjeldahl Determination for Nitrogen

Det.	Wt. of Sample	0.0942 N HCl	Per Cent Nitrogen
I	0.4043 g.	57.68 cc.	18.8
II	0.2938 g.	42.68 cc.	19.2
III	0.3901 g.	54.18 cc.	18.3
IV	0.3404 g.	49.27 cc.	19.1

A blank was run and corrections were made accordingly.

A consideration of all compounds that can be reasonably expected to be present in the reduction mixture as a result of hydrogenolysis was undertaken.

Possible Compounds	Empirical Formula	Mol Wt.	% Nitrogen (Calc.)
$C_5H_{10}NCH_2\underset{NH_2}{C}(CH_3)CH_2NC_5H_{10}$	$C_{14}H_{29}N_3$	239.39	17.55
$C_5H_{10}NCH_2\underset{NH_2}{CH}(CH_3)$	$C_8H_{18}N_2$	142.24	19.696
$C_5H_{10}NCH_2\underset{NH_2}{C}(CH_3)CH_3$	$C_9H_{20}N_2$	156.27	17.866

The results of the analyses indicate that the low boiling fraction may be 1-piperidino-2-aminopropane.

Condensation of Diethylamine with Formaldehyde and Nitroethane

Cerf de Mauny (19) reported the preparation and reduction of 1,3-diethylamino-2-nitropropane but did not mention any condensations involving nitroethane with diethylamino methanol. A search through the literature proved to be unsuccessful.

Experiment 1.

To 35 cc. of a cold solution of 37% formaldehyde was added dropwise 21.4 g. of cooled diethylamine. Fifteen grams of nitroethane was then added to this mixture with stirring. After standing for about an hour, two layers appeared, the upper layer greenish in color, soluble in ether, while the lower layer was colorless, insoluble in ether, but soluble in water. The upper layer was separated off. The lower layer was extracted with ether and the ether extracts combined with the upper layer. The ether was distilled off and the residue distilled at 3 mm. pressure.

At first, drops distilled over at 69-71°C. The boiling point varied with the temperature of the oil-bath. Later, on, in the distillation, the liquid distilled at 65°C. regardless of the temperature of the oil-bath. About 10 to 15 cc. remained behind which on further heating distilled at 123-125°C., while the oil-bath was at 178-182°C.

Fraction	Weight	Boiling Point	Oil-Bath Range
I	24.1 g.	69-71 65	100-105 110-120
II	4.5 g.	123-125	178-182

Fraction I was insoluble in sodium hydroxide but dissolved in 10% hydrochloric acid solution with the evolution of white fumes. This indicated the presence of amine groups. This fraction was then treated with aluminum amalgam for reduction.

Experiment 2.

To 79 cc. of a cold solution of 37% formaldehyde was added dropwise 42.6 g. diethylamine. Thirty g. of nitroethane was then added. After thorough mixing the mixture was allowed to stand for two hours. The upper layer was separated off, dissolved in the ether extracts of the lower layer and the solution dried over anhydrous sodium carbonate. The ether was removed and the residue distilled under reduced pressure.

Fraction	Weight	Boiling Point	Oil-Bath	Pressure
I	41.3 g.	71-73	110-112	1 mm.
II	6.0 g.	65-68	112-115	2 mm.
III	7.2 g.	100-120-138	165-200-210	2 mm.

Description: A small amount of liquid came over at room temperature and before Fraction I was obtained..The residue was approximately 1-2 g. and the trap had one gram of liquid. Fraction I was redistilled at 0.5 mm. and was obtained at 61-63°C.

Fraction I was divided into portiona and some of them were reduced. Other portions were used for analysis.

An analysis of Fraction III was also made.

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